

REMARKS

Claim Amendments

Claim 1 has been amended to recite that the vector constructs are replication incompetent vector constructs. Support for this amendment can be found, *inter alia*, in Example 9, which demonstrates the constructs are not replication competent.

Rejection of Claims 1-5, 12-13, and 26-29 under 35 U.S.C. 112

Claims 1-5, 12-13, and 26-29 stand rejected as being indefinite for use of the term non-replicating. The term is no longer present in the claims. The rejection is moot.

Rejection of Claims 1-5, 12-13, and 26-29 under 35 U.S.C. 103(a)

Claims 1-5, 12-13, and 26-29 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 95/07994 (“Dubensky”), in view of Hu et al. AIDS Res. Hum. Retrovir., Vol. 7(7), 615-620 (“Hu”).

Dubensky is cited for teaching the “use of live recombinant alphavirus to stimulate immune responses which are either replication competent or replication defective.” Office Action at page 5. Hu is cited for teaching “the benefits of ‘boosting’ a live recombinant virus immunization with the immunizing protein itself instead of with a second immunization with the recombinant virus.” Office Action at page 6. The Office Action further contends that Dubensky “provides motivation for following a prime and boost protocol to induce an antigen specific immune response.” *Id.* This motivation is

based on Dubensky's teaching of sequential immunization with the same vector, which the Office Action characterizes as "prime and boost using the same vector." *Id.* Finally, the Office Action contends that "the skilled artisan would have had a reasonable expectation of success in generating an immune response by administering a 'non-replicating' vector construct encoding a viral antigen followed by or preceded by administration of the viral antigen itself." Office Action, paragraph spanning pages 7-8. Applicants traverse.

The skilled artisan would have had no motivation to combine the teachings of Dubensky and Hu and, moreover, would have had no reasonable expectation of success in doing so.

A. Replication competent

As an initial matter, Applicants would like to clarify the meaning of various terms relating to reproduction of virus, viral nucleic acid and expression of proteins from these. First, the term **replication competent** refers to the ability of a viral vector to undergo complete reproduction of the viral particle, leading to the production of infectious viral progeny.¹ Thus, following infection of a target cell, a replication competent viral vector drives amplification of viral nucleic acid and expression of viral enzymes necessary to produce structural proteins and assembly or packaging of viral elements into infectious virions. The infectious virions are capable of re-infection and replication of the viral cycle in adjacent cells.

B. Replication incompetent (replication defective)

In contrast, a **replication incompetent** viral vector is only capable of a single round of infection. Replication defective is synonymous with replication incompetent.

¹ See, for example, Example 9 of the specification discussing replication competent infectious virus.

Although unable to produce infectious virus, replication incompetent vectors may contain nucleic acids that are amplified within the infected cell and from which encoded protein is expressed.

Applicants traverse with respect to the motivation asserted by the Office Action. A sequential immunization strategy using two identical virus immunizations provides no motivation for a prime and boost strategy using virus and protein immunizations. In Dubensky the immune system pathways stimulated by using the same vector twice would be identical. The skilled artisan reading Dubensky would not engage in a deductive leap between the application of repeated doses of identical virus to dosing with virus followed by protein, modalities which the skilled artisan would have understood to effect *different* immune pathways.

The skilled artisan reading Dubensky in view of Hu would be further dissuaded from using repeated virus immunizations. Hu teaches that while earlier experiments had a modest increase in antibody response, vaccinia prime followed by vaccinia boost was ineffective in these experiments. Hu at page 618, ¶ 3.

Further, because repeat vaccinations using replication incompetent alphavirus give improved immune responses, the skilled artisan would not extrapolate from two virus immunizations to a prime and boost approach. Applicants enclose alphavirus studies by Greer,² and White,³ which establish that repeated alphavirus immunizations give enhanced responses. Greer used a Venezuelan Equine Encephalitis (VEE)

² Greer CE, Zhou F, Legg HS, Tang Z, Perri S, Sloan BA, Megede JZ, Uematsu Y, Vajdy M, Polo JM. A chimeric alphavirus RNA replicon gene-based vaccine for human parainfluenza virus type 3 induces protective immunity against intranasal virus challenge. *Vaccine*. 2007 Jan 5;25(3):481-9. (Copy enclosed with IDS).

³ White LJ, Parsons MM, Whitmore AC, Williams BM, de Silva A, Johnston RE. An immunogenic and protective alphavirus replicon particle-based dengue vaccine overcomes maternal antibody interference in weanling mice. *J Virol*. 2007 Oct;81(19):10329-39. (Copy enclosed with IDS).

alphavirus vector in a prime and boost protocol and found a doubling of antibody titers. Compare Figure 2B (Greer at page 484, Col. 2) doses 10^6 and 10^7 in the “Post 1st” and “Post 2nd” columns, which show approximately a 2-fold increase in both IgG1 and IgG2a levels. White obtained similar benefits using alphavirus prime and boost. White primed at week 3 with DENV2-VRP (Venezuelan Equine Encephalitis Replicon Particle expressing Dengue Virus antigens from the DENV2 strain) and boosted at week 15 with the same vector. The data at week 15 shows that the boost increased the anti-DENV2-VRP titer from $10^{4.3}$ to $10^{4.8}$. See White at page 10333, col. 1, Figure 2A. White stressed the importance of the improved response using repeated virus immunizations: “It is important to note that, in spite of the antivector response after the prime, a booster response to the DENV protein was not hampered (Fig. 2B).” White at page 10334, col. 2. In contrast, replication incompetent vaccinia virus does not give an improved response in a prime/boost protocol because of anti-vector immunity.

Hu’s approach makes sense in the context of vaccinia virus where neither replication competent nor replication incompetent vector can be used repeatedly, as further demonstrated by Sharpe,⁴ because anti-vector responses prevent improved immune responses. But vaccinia’s defects as a vector are not observed in alphaviruses, which provide improved immune responses on repeated immunization. Accordingly, Dubensky’s sequential vaccination strategy using alphaviruses provides no motivation for

⁴ Sharpe S, Polyanskaya N, Dennis M, Sutter G, Hanke T, Erfle V, Hirsch V, Cranage M. Induction of simian immunodeficiency virus (SIV)-specific CTL in rhesus macaques by vaccination with modified vaccinia virus Ankara expressing SIV transgenes: influence of pre-existing anti-vector immunity. *J Gen Virol.* 2001 Sep;82(Pt 9):2215-23. (Copy enclosed in IDS).

Sharpe illustrates that repeated immunizations result in a deteriorating response: “In animals immunized with MVA-SIVmacJ5 constructs, neutralizing antibodies were detected only after the second immunization (titres 19-46). By the time of the third vaccination, titers had dropped below the limit of detection.” Sharpe at page 2218, col. 1.

virus prime and protein boost much less protein prime and virus boost.

The Office contends that “the skilled artisan would have had a reasonable expectation of success in generating an immune response by administering a ‘non-replicating’ vector construct encoding a viral antigen *followed by or preceded* by administration of the viral antigen itself.” Office Action, paragraph spanning pages 7-8. (emphasis added).

The skilled artisan reading Hu could not have a reasonable expectation of success in extrapolating from a replication competent vector to a replication incompetent vector in the prime boost protocol.

The Office Action asserts that Hu did not refer to the replication status of the recombinant vaccinia virus. Office Action at page 6. Hu’s vaccinia virus, however, is replication competent. Hu’s Table 1 at page 617 notes at footnote b that the recombinant virus “used in all experiments described here is a derivative of v-NY,... This recombinant has also been referred to as v-env (NY) or HIVAC-1e.” With respect to HIVAC-1e, Hu cites to a 1991 paper by Cooney *et al.* titled “Safety of and immunological response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein”⁵ (“Cooney 1991”). Cooney 1991 teaches that HIVAC-1e used in the cited Hu reference is an infectious, replication competent virus. Cooney 1991 states that: “The use of a gauze and non-permeable opsite dressing to cover the vaccination site effectively contained replicating virus, thereby preventing environmental contamination and person-to-person spread of vaccine virus.” Cooney 1991 at page 571, col. 2, ¶ 1. Thus, the data generated

⁵ Cooney EL, Collier AC, Greenberg PD, Coombs RW, Zarling J, Arditti DE, Hoffman MC, Hu SL, Corey L. Safety of and immunological response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein. *Lancet*. 1991 Mar 9;337(8741):567-72. (Copy enclosed with IDS).

derives from an infectious virus and the assertion that Hu's vaccinia virus is not replication competent cannot stand. Hu stands for the teaching of viral replication in replication competent virus. Hu does not teach a replication incompetent virus or viral vectors.

There can be no reasonable expectation of success because the immunology of a replication competent virus differs greatly from a replication incompetent virus. The skilled artisan obtaining an immune response with a virus that produces infectious progeny would not have expected a similar immune response using a vector construct that fails to produce any viral particles; *i.e.*, a vector construct that is replication incompetent. Replication competent virus undergoes repeated cycles of infectivity, leading to exponential-like intracellular and extracellular exposure of virally-expressed proteins. In contrast, a replication incompetent vector produces protein only inside the first cell infected and produces no infectious viral particles at all, and certainly none that escape from the cell. These vaccination approaches are not sufficiently analogous immunologically such that a skilled artisan would have expected that they were interchangeable. Indeed, the discussion of White, Greer, and Sharpe above further emphasizes the immunological differences that prevent predictability of results with these viral systems.

Hu's results further support this conclusion. Hu does not teach a prime-boost system that is capable of generating antibody regardless of the ordering of protein and vector injections. Hu teaches that when a replication competent vaccinia virus is followed by a protein injection, elevated antibody is produced. In marked contrast, however, Hu teaches that if the protein is injected first there is no increase in antibody

production. See Animal Group 3 of table 1 on page 617. Therefore, the only working approach Hu teaches is the use of replication competent viral vector followed by a protein boost. Hu also demonstrates that the immune response stimulated by vaccination with replication competent vaccinia virus is complex. The skilled artisan would recognize that Hu's teachings must be interpreted narrowly to apply only to replication competent vaccinia virus delivered before a protein boost. Indeed, later work by the same group—"Cooney 1993,"⁶ which includes Hu as an author—emphasizes that expecting success using replication incompetent viral vectors would have been unreasonable. In Cooney 1993, published two years after Hu, the replicating HIVAC-1e vaccinia virus was used in a prime-boost protocol. The authors concluded that:

[T]he use of combination vaccines regimens, consisting of priming with a *live* recombinant vaccinia virus expressing a HIV subunit protein (or possibly alternate *live* vectors such as avipox, adenovirus, or bacillus Calmette-Guérin) followed by boosting with soluble recombinant protein warrants further study for the development of an immunization strategy for HIV.

Cooney 1993 at page 1886, col.1, ¶ 4. (emphases added).

Cooney 1993 thus offers only other live, replication competent viruses as an alternative to vaccinia. Replication of the virus was important in Cooney 1993 because they considered that decreased replication negatively affected priming and was therefore to be avoided. They noted that "one potential obstacle to the general use of a recombinant HIV-1 vaccinia vaccine is that preexisting immunity to vaccinia can *limit its replication and therefore interfere with priming* to the nonvaccinia antigens expressed by

⁶ Cooney EL, McElrath MJ, Corey L, Hu SL, Collier AC, Arditti D, Hoffman M, Coombs RW, Smith GE, Greenberg PD. Enhanced immunity to human immunodeficiency virus (HIV) envelope elicited by a combined vaccine regimen consisting of priming with a vaccinia recombinant expressing HIV envelope and boosting with gp160 protein. Proc Natl Acad Sci U S A. 1993 Mar 1;90(5):1882-6. (Copy enclosed with IDS).

the recombinant vector.” Cooney 1993 at page 1882, col.1, ¶ 2. (emphasis added). Cooney 1993 thus teaches that any factor that leads to a decrease in viral replication was to be avoided. Cooney 1993 emphasizes that only replication competent viral vectors are suitable for prime boost protocols.

Immune systems are extremely complex. The state of the art with respect to prime boost at the time of invention shows that only replication competent vectors were considered suitable. It also teaches that replication incompetence was to be avoided because the expectation was that decreased replication would inhibit priming. In view of these teachings, the skilled artisan would not reasonably expect that Hu’s prime-boost approach could be applied to replication incompetent viral vectors with an expectation of success.

Dubensky and Hu, alone or in combination, neither supply any motivation to perform the method of generating an immune response that is the subject matter of claim 1, nor provide the skilled artisan with any reasonable expectation of success in doing so. Dubensky does not teach prime and boost. Dubensky does not teach replication competent vectors. Hu teaches replication competent vectors in a prime-boost approach, but does not teach or suggest using replication defective vectors.

Any combination of Dubensky and Hu must ignore Hu’s requirement that replication competent virus is used and also ignore Dubensky’s requirement that only repeated vector immunization is used in their procedure. The only blazemark leading to the combination of these references is found in applicants own disclosure. Such hindsight is impermissible.

Applicants therefore respectfully request withdrawal of the rejection.

Dated: May 12, 2008

Customer No. 22907

Respectfully submitted,
BANNER & WITCOFF, LTD.

By: /Lisa M. Hemmendinger/, Reg.
No. 42,653

for Dale H. Hoscheit
Registration No. 19,090